PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MANCINI, Vincenzo
Ing. A. Giambrocono & C. s.r.l.
Via Rosolino Pilo, 19/B
I-20129 Milan
ITALIE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.10.2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
VM/gf G69064	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/12889	18.11.2003	16.01.2003

Applicant
NEWRON PHARMACEUTICALS SPA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Sleex, C Tel. +49 89 2399-8044

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference VM/gf G69064	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12889	International filing date *(day/month/year)* 18.11.2003	Priority date *(day/month/year)* 16.01.2003
International Patent Classification (IPC) or both national classification and IPC A61K31/165		
Applicant NEWRON PHARMACEUTICALS SPA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.05.2004	08.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Albayrak, T Telephone No. +49 89 2399-7549

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12889

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-13 received on 21.09.2004 with letter of 20.09.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9-13

   because:

   ☒ the said international application, or the said claims Nos. 9-13 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-13
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-8
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Re Item I

Basis of this report are pages 1-16 of the application as originally filed and claims 1-13 as received on 21.09.2004.

Re Item III

The subject-matter of claims 9-13 is related to subject-matter considered to be covered by the provisions of Rule 67.1 (iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4) (a) (I) PCT).

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: WO 99/35125 A (PEVARELLO PAOLO ;VARASI MARIO (IT); NEWRON PHARM SPA (IT); SALVATI) 15 July 1999 (1999-07-15)
D2: WO 99/26614 A (CAI SUI XIONG ;LAN NANCY C (US); COCENSYS INC (US); WANG YAN (US)) 3 June 1999 (1999-06-03)
D3: EP-A-1 123 702 (EISAI CO LTD) 16 August 2001 (2001-08-16)

1. **Novelty**

Amended claims 1-13 are directed to the use of α-aminoamides for the preparation of a medicament for the treatment of head pain conditions **involving a cerebral vasodilatation mechanism**.

- D1 discloses the claimed compounds as analgesic agents. Among the disclosed pain conditions none relying on cerebral vasodilation mechanisms is explicitly mentioned.
  Taken into consideration applicant's submitted documents it is clear, that pain conditions involving a cerebral vasodilatation mechanism are to be regarded as a specific group of pain conditions.
  Thus, D1 does not anticipate any of claims 1-13.

- Neither D2 nor D3 specifically discloses the claimed compounds for the treatment of head pain conditions involving a vasodilatation mechanism.
  Thus, neither D2 nor D3 anticipate any of claims 1-13.

Therefore, claims 1-13 are regarded as being novel over the cited prior art (Art.

33(2) PCT).

2. Inventive step

The problem underlying the present application is the provision of compounds for the treatment of head pain conditions involving a vasodilatation mechanism.

The solution, according to the applicant lay in the provision of compounds as claimed.

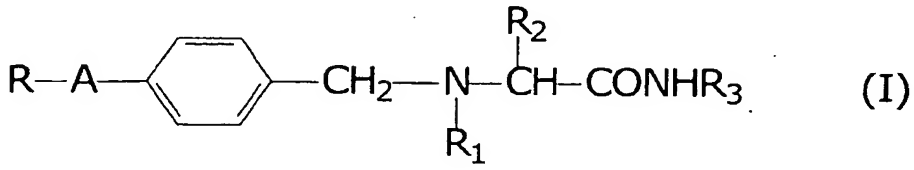
D2 discloses a broad formula including the claimed α-aminoamides for the treatment of migraine. Migraine is a head pain condition involving a vasodilatation mechanism.

However, from the present description experimental data are available which show, that **not all** compounds of D2 are useful in the preparation of a medicament for treating head pain conditions involving a vasodilatation mechanism.
The skilled person, confronted with the problem would not find any hint in the prior art which would suggest to select the group of compounds as claimed.

Therefore, an inventive step under Art. 33(3) PCT is acknowledged for present claims 1-13.

CLAIMS

1. Use of an α-aminoamide of formula (I):



(I)

wherein:

A is a $-(CH_2)_m-$ or $-(CH_2)_n-X-$, wherein m is 1 or 2; n is zero, 1 or 2; and X is -O-, -S- or -NH-;

R is a furyl, thienyl, or pyridyl ring or a phenyl ring, unsubstituted or substituted by one or two substituents independently selected from halogen, hydroxy, C_1-C_4 alkyl, C_1-C_3 alkoxy and trifluoromethyl;

R_1 is hydrogen or C_1-C_3 alkyl;

R_2 is hydrogen or C_1-C_2 alkyl, unsubstituted or substituted by hydroxy or phenyl; phenyl, unsubstituted or substituted by one or two substituents independently selected from C_1-C_3 alkyl, halogen, hydroxy, C_1-C_2 alkoxy or trifluoromethyl;

R_3 is hydrogen or C_1-C_3 alkyl;

if the case, either as a single isomer, or as a mixture thereof, or a pharmaceutically acceptable derivative thereof;

in the manufacture of a medicament for the treatment of head pain conditions involving a cerebral vasodilatation mechanism.

2. Use of an α-aminoamide according to claim 1, wherein in formula (I):

A is a group selected from $-CH_2-CH_2-$, $-CH_2-O-$, $-CH_2-S-$, $-CH_2-CH_2-O-$;

R is a phenyl ring, unsubstituted or substituted by one or two substituents independently selected from halogen, C_1-C_3 alkyl or a methoxy group; or a thienyl ring;

R_1 is hydrogen or C_1-C_2 alkyl;

R_2 is hydrogen or methyl, unsubstituted or substituted by hydroxy, or phenyl unsubstituted or substituted by C_1-C_2 alkyl, halogen, hydroxy, methoxy or trifluoromethyl; and

R_3 is hydrogen or C_1-C_2 alkyl.

3. Use of an α-aminoamide according to claim 1 or 2, wherein in formula (I):

A is $-CH_2-O-$, $-CH_2-S-$ or $-CH_2-CH_2-$;

R is a phenyl ring, unsubstituted or substituted by one or two halogen atoms;

R_1 is hydrogen;

R_2 is hydrogen or methyl, unsubstituted or substituted by hydroxy or phenyl ring, unsubstituted or substituted by a halogen atom; and

R_3 is hydrogen or methyl.

4. Use of an α-aminoamide according to claim 1, wherein the α-aminoamide is selected from:

2-(4-benzyloxybenzylamino)propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(3-chlorobenzyloxy)benzylamino]propanamide;

2-[4-(4-fluorobenzyloxy)benzylamino]propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-N-methyl-propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-N-methyl-propanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-3-hydroxy-propanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxy-propanamide;

2-(4-benzyloxybenzylamino)-3-hydroxy-N-methylpropanamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(2-chlorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-[4-(3-chlorobenzyloxy)benzylamino]-3-hydroxy-N-methylpropanamide;

2-(4-(2-thienylmethylenoxy)benzylamino)-propanamide;

2-[4-(2-(3-fluorophenyl)ethyl)benzylamino]-propanamide;

2-[4-benzylthiobenzylamino]-propanamide;

2-[4-benzyloxybenzylamino]-3-phenyl-N-methylpropanamide;

2-[4-benzyloxybenzylamino] N-methylbutanamide;

2-[4-benzyloxybenzylamino]-2-phenyl-acetamide;

2-[4-(2-fluorobenzyloxy)benzylamino]-2-phenyl-acetamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-2-phenyl-acetamide;

2-[4-(3-chlorobenzyloxy)benzylamino]-2-phenyl-acetamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-2-(2-fluorophenyl)-acetamide;

2-[4-(3-fluorobenzyloxy)benzylamino]-2-(3-fluorophenyl)-acetamide;

2-[4-(3-chlorobenzyloxy)benzylamino]-2-(3-fluorophenyl)-acetamide;

if the case, either as a single isomer or as a mixture thereof, or a pharmaceutically acceptable derivative thereof.

5. Use of an α-aminoamide according to any of the previous claims, wherein the α-aminoamide is selected from: (S)-(+)-2-[4-(3-fluorobenzyloxy)benzylamino]-propanamide, (S)-(+)-2-[4-(2-fluorobenzyloxy)benzylamino]-propanamide and (S)-(+)-2-[4-(3-chlorobenzyloxy)benzylamino]-propanamide.

6. Use according to any of the previous claims, wherein head pain conditions are both primary and secondary headache disorders.

7. Use according to any of the previous claims, wherein head pain conditions include migraine, headache, hemicrania.

8. Use according to any of the previous claims, wherein migraine is acute, transformed or vascular migraine; headache is acute, cluster, evolutive or tension type headache; hemicrania is chronic paroxysmal hemicrania.

9. A method for the treatment of head pain conditions involving a cerebral vasodilatation mechanism in a mammal in need thereof comprising administering to the mammal a therapeutically effective dose of at least one α-aminoamide of formula (I) as defined in any of claims 1 to 5.

10. A method according to the previous claim, wherein the mammal is administered a dose of the α-aminoamide of formula (I)

as defined in any of claims 1 to 5 which ranges from about 0.05 to 20 mg/kg body weight per day.

11. A method according to claim 9 or 10, wherein the mammal is administered a dose of the α-aminoamide of formula (I) as defined in any of claims 1 to 5 which ranges from about 0.5 to 10 mg/kg day.

12. A method according to any of claims from 9 to 11, wherein the mammal is administered a dose of the α-aminoamide of formula (I) as defined in any of claims 1 to 5 which ranges from about 0.5 to 5 mg/kg day.

13. A method according to any of claims from 9 to 12, wherein the head pain conditions are as defined in any of claims 6 to 8.